General information

Date:
Nov 2021

Title of study:
Computed tomography estimated right ventricular function and exercise capacity in patients with continuous-flow left ventricular asssist devices.

Clinical trials identifier:
NCT02658136

Trial editor
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Time Schedule
Period of inclusion: 01.12.2015 (or when the protocol is approved) until 19 participants are enrolled in the trial. The estimated duration of the trial is two years.

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The Ethics Committee
Videnskabelig Etisk Komité. Region Hovedstaden, Hillerød, Denmark.

Study protocol background

Introduction to mechanical circulatory support (MCS).

When pharmacological therapy becomes insufficient in advanced end-stage heart failure (HF) transplantation remains the gold standard of therapies. However, due to a severe lack of donor organs, MCS is an alternative option for some eligible patients. Mechanical circulatory support in the form of a left ventricular assist device is a pump supporting the left ventricle by pumping blood from the apex to the ascending aortae. The pump is powered by externally placed batteries that are connected to the pump by a driveline penetrating the abdominal wall (Figure 1). Today we only use continuous-flow left ventricular assist devices (CF-LVAD) based upon results from clinically controlled trials. The CF-LVAD can be utilized either as a bridge-to-transplantation (BTT) or as life-long support called destination therapy (DT). Implantation with a CF-LVAD increases survival and improves quality of life (1). In addition functional status is improved post-implant, however, it is not normalized and peak oxygen uptake (peak VO2) remains severely reduced (2). At University Hospital Rigshospitalet we use a CF-LVAD called the HeartMate II and lately also it's successor the HeartMate III. The number of implantations is markedly increasing (3) and this fact underlines the need to monitor the treatment carefully which includes focus on optimizing QOL and limitting the extent of adverse events. While the effect of right ventricular (RV) failure early after pump implantation, and its effect on outcome has been extensively studied (4-6), the effects of late RV failure on exercise capacity and QOL has been sparsely described. Thus the purpose of this study is to examine RV function and the association to exercise capacity in CF-LVAD patients.

Right ventricular function and pulmonary circulation.

A well functioning RV is of crucial importance in HF patients eligible for a CF-LVAD (5). In the abscens of shunts total cardiac output (TCO) will equal RV output and is provided solely by the device when the aortic valve (AV) is closed. As TCO is dependent on RV output the latter is a potential limiting factor in a required exercise-induced increase in cardiac output.

Unloading the left ventricle with a CF-LVAD results in immediate increased preload and decreased afterload on the right side that can result in initial worsening RV function early after implant. Subsequently, with RV adaptation, the decreased right-sided filling pressures will frequently lead to improvements in RV function for example demonstrated by diminished tricuspid regurgitation (TR). In contrast when persistent impaired RV contractility develops it is often secondary to onset of pulmonary artery hypertension or disadvantageous alterations in the mechanical interventricular relationship post-implant. Also intraoperative RV injury exposes a risk of developing RV failure (4, 7-9).

Defining RV failure

Variuous definitions of RV failure is used but will often include some of the following: Need for inotropic agents > 14 days postoperatively, use of pulmonary vasodilators such as inhaled nitric oxide > 48 hours, central venous pressure > 18 mmHg and cardiac index <2.3 l/min/m2 (with normal left atrial - or pulmonary capillary wedge pressure) and/or the need for RV circulatory support/asssist device. Depending on the defining criteria the incidence of RV failure after LVAD implantation varies considerably from 5-44% (5, 7, 10-13).

Previous research on RV function and exercise capacity in LVAD patients.

In HF patients without mechanical circulatory support preserved RVEF has previously been shown to be significantly associated with higher peak %VO2 but not peak VO2 (14). Post-implant a small study found that poor RV function (defined as RV fractional area change) and limited reduction in pulmonar vascular resistence (PVR) was associated with shorter 6-minute walking distance (15). Another study found late-onset RV failure (defined as RV stroke work index < 4.0 g/m2 at all rotational speeds) to be significant associated with 6-minute walking distance and peak VO2 at three months post-implant (16). Raina et el found that pre-operative poor functional class (~INTERMACS score) was significant

associated to post-operative RV failure (17). In contrast Baumwol et al did not find a difference in post-implant NYHA classification between patients with and without RV failure (13). In a pioneering study of exercise capacity in the formerly used pulsatile LVADs Jaski et al found that despite a decrease in RV end-diastolic dimension, RV stroke volume showed a trend toward being higher with exercise compared with baseline. They concluded that increases in systemic flow with exercise appear to be limited by the pulsatile flow-LVAD complex and not by intrinsic RV function (18). Our group has formerly, in a subanalysis, examined the relationship between echocardiographic measures of RV function *during rest* and exercise capacity and found no association (19). However, as described below, echocardiography in CF-LVAD patients can be challenging, especially measuring parameters of RV function.

Assessment of RV function in CF-LVAD patients.
Echocardiographic signs of decreasing RV function are amongst others progressive TR, increasing RV size, limited RV fractional area change (RVFAC), increasing tricuspid annular plane systolic excursion (TAPSE), increased right atrial pressure and decreased global longitudinal strain of the RV free wall (10, 15, 17, 20-22). However, due to the positioning of the CF-LVAD inflow cannula (especially in the HeartMate III) it is challenging to obtain images from the apical view and thus visualizing the right-sided free wall. Assessing RV function by magnetic resonance (MR) is gold standard (23) but is contraindicated with a CF-LVAD in situ. However, multi-detector computed tomography (MDCT) is shown to be comparable to MR in assessing RV function (24). Right ventricular ejection fraction (RVEF) by MDCT is highly reproducible (interobserver variablity 0.89 and intraobserver variablity 0.99) and is not affected by acoustic windows. The echo-derived variable that best correlates with MDCT RVEF is M-mode RVFAC (23, 24). Thus to estimate RV function in this study we will, in addition to echocardiography, undertake cardiac computed tomography (CCT).

Hypothesis
Poor function of the right ventricle during exercise is related to exercise intolerance in CF-LVAD patients.

Primary endpoint
- Right ventricular ejection fraction during rest and exercise estimated by CCT.
- Cardiopulmonary exercise testing (CPET) measuring peak oxygen uptake (peak VO2) in ml/kg/min.

Methods
Study cohort
Stable HF patients with a CF-LVAD either as BTT or as DT. Before commencement of the study the protocol will be approved by the Local Ethics Committees. The trial will be registered at www.clinicaltrials.gov.

Inclusion criteria
- Outpatients from Department of Cardiology, University Hospital of Copenhagen, Rigshospitalet, Denmark.
- Age ≥ 18 years.
- Ischemic or non-ischemic cardiomyopathy.
- Signed informed consent.

Exclusion criteria

- Unstable patients with the need for intravenous inotropic therapy.
- CF-LVAD implantation less than one month ago.
- eGFR < 45 ml/min.
- Contrast allergy.

Statistics
The primary outcome of this study is to describe the association between CCT-derived RVEF and peak VO2 during exercise. Previous analyzes have estimated a 7.7% standard deviations in RVEF and 6.3 ml/kg/min in peak VO2 in CF-LVAD patients (19, 23). As the current study is explorative we are not guided from previous studies on the correlation between RVEF and peak VO2 but we estimate that including 15 patients will suffice. Analyses will be performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, North Carolina). Statistical significance will be defined as a two-tailed *p* value below 0.05. Differences between groups will be assessed using paired or unpaired t-tests as appropriate. Continuous variables will be expressed as mean ± standard deviation if parametric, if non-parametric as median and interquatile range. Categorical variables will be described with frequency and percentage. Relation between continuous variables will be calculated as correlation coefficients, if data are parametric distributed using Pearson´s coefficient and otherwise Spearman's rank correlation coefficient.

Interventions
1/ Cardiac Computed Tomography (CCT)
Using ECG-gated CCT (320-slice MDCT Toshiba VISION Edition Aquilion One Scanner) we will measure RVEF, RV end-diastolic and end-systolic volumes (RVEDV and RVESV) and peak diastolic filling rates (dV/dt). The same variables will be measured on the left side. Further we will estimate the position of the CF-LVAD cannulas. The analysis of the images will be performed by the Cardiac-MDCT Research Unit at Rigshospitalet by means of Vitrea software (Vital images, USA). In each patient we will undertake two sequential CTs – one at rest and one immediate after two minutes of supine 25 Watt ergometer bike exercise (attaching a pair of foot pedals to the bedside in the examination room). If exercise testing, against expectations, is not possible due to technical limitations we will instead induce stress with a dobutamine infusion protocol (se details below). The CCTs will be undertaken with intravenous contrast injections in a big vein in the right elbow flexion; 5-6 ml/second and subsequently the retrospective scans will be performed. The total contrast dose will be 140 ml and the total radiation dose a maximum of 20 mSv. As defined in the section on “exclusion criteria” eGFR must be ≥ 45 ml/min.

Dobutamine stress test (Secondary choice if exercise in CT room is not possible).
A dobutamine stress test can be used if we are unable to undertake exercise in the CT room due to technical/space challenges. Dobutamine will mimic the effects of exercise on the heart by direct ß1 and ß2 stimulation with a dose-related increase in heart rate, blood pressure, and myocardial contractility. An intravenous line will be started in the patient´s left arm for injection of the dobutamine and an infusion pump will be connected. The dobutamine infusion will begin at a rate determined by the patient´s weight (Figure 2). The rate of the infusion will be increased every third minute until the target heart rate (determined by the doctor based on age and physical condition), or until the maximum dose of dobutamine has been reached (40 ug/kg/min). Plasma half-life of dobutamine is 2-3 minutes. Contraindication for dobutamine infusion is recent myocardial infarction, unstable angina, uncontrolled hypertension (>200/110 mmHg), severe aortic stenosis, atrial tachyarrhythmia with uncontrolled ventricular response and unwillingness to give consent. After dobutamine infusion is started the patient will be monitored continuously with evaluation of blood pressure, symptoms and ECG tracing. Post-stress the patient is monitored for a minimum of 10 minutes and until symptoms are resolved.

2/ Cardiopulmonary exercise testing (CPET)
Cardiopulmonary exercise testing will be performed on an upright ergometer bicycle (Schiller CS-200, Schiller AG, Bar, Switzerland). Calibration before each test for gas, ambient conditions and flow, according to manufacturer´s instructions, will be performed. Breath-by-breath respiratory gas analysis measuring oxygen consumption (VO2), carbon dioxide excretion (VCO2) and expiratory minute ventilation (VE) will be undertaken. Peak oxygen uptake will be calculated as ml/kg/min. The participants will be encouraged to keep cycling until exhaustion and will be monitored with pulse oximetry and continuous 12-lead electrocardiogram during the exercise. Peak heart rate will be measured at the same time as peak VO2. The aim of exercise duration is 8-10 minutes and based upon prior experience the protocol starts at 25 Watt followed by 10 Watt increase/1 minute. The pedaling rotation will be maintained at 60-70 rpm.

3/ Transthoracic echocardiography
Echocardiography is performed, prior to CPET, according to current guidelines (11, 25) on an Philips iE33 cardiac ultrasound system (Philips Healthcare, Best, the Netherlands). The examination will include 2D, tissue doppler imaging (TDI) and pulsed –and continuous wave Doppler images that will be aquired in the parasternal long-axis view and in the apical 4 chamber and 5 chamber views. A minimum of three echocardiographic cine loops will be stored digitally for offline analysis using Philips Xcelera analysis software version 3.1. Echocardiograms will be analyzed by a reader blinded to clinical outcomes. Focus will be on measuring the following parameters: Tricuspid regurgitation (defined as; 0= none, 1= mild, 1.5= mild-moderat, 2= moderat, 2.5= moderat-severe and 3=severe), TAPSE (measured by M-mode from an apical RV view), RVFAC and estimates of right atrial pressure (obtained from inferior vena cava from subcostal view). Aortic valve opening and a potential LV recovery will also be evaluated.

4/ Blood sampling
As the first thing on the day of the study a blood sample will be drawn from a peripheral vein. A total of no more than 45 ml is collected at one time; 25 ml is directly analyzed for lactate dehydrogenase, haptoglobin, free plasma hemoglobin, hemoglobin, INR, platelets, lactate, creatinine, eGFR, amylase, AST, ALT, bilirubin, potassium, calcium, sodium, cholesterol, leukocytes, CRP and pro-BNP. After the direct analysis the sample will be destroyed.
The remaining 20 ml is stored in an approved biobank and subsequently analysed for Mid-regional pro-atrial natriuretic peptide (MR-proANP) , Copeptin, Mid-regional pro-adrenomedullin (MR-proADM) and C-terminal pro-endothelin-1 (se details in the section “Biobank: Handling of biological material” below).

<u>Radiation hygiene</u>
Under the two CCT scans each patient will receive a total radiation dose of a maximum of 20 mSv depending on weight, heart rate and rhythm during the scan. It can be calculated that, theoretically, the lifetime risk of developing a deadly cancer increases by 0.05% for each 10 mSv the patient receives. Thus the lifetime risk of dying of a cancer increases from 25% to 25.1% in each patient.
Sivert definition: 1 Sivert is the radiation hygienic measure of the biological effect of one dose ionizing radiation. Other terms for the same is “dose equivalent” and “effect dose”. 1 Sv = 1 Sivert = 100 rem = 1 J/kg (Calculation by “Statens Institut for Strålebeskyttelse).
4/ Risks associated with a dobutamine stress test: Chest pain, high blood pressure, palpitations, irregular heartbeats, dizziness and nausea.

Reporting adverse events /side effects
All events during the trial which might constitute a safety concern for the participant or jeopardise the execution of the trial will be reported to the Ethics Committee immediately.

Ethical considerations
The trial will be initiated following approval from the Ethics Committee and from the Data Protection. The trial will comply with the requirements stated in the Declaration of Helsinki II. As described we estimate that the rarely seen risks and side effects are easily justified by the potential benefits for the participants. Trial participants will receive adequate information on the purpose, metod, advantages and risks associated with participating in the trial (orally and in writing). Before participants are included we will collect an informed written consent. Participants are furthermore informed that it is possible to withdraw from the trial at any given time and that this decision will have no effect on future treatment and follow-up.

Informed consent
Patients that are supported with a CF-LVAD can participate in the study if they meet all the inclusion - and exclusion criteria listed above. Before contacting the patients we will seek information on exclusion criteria in the patient records. Information can be passed from physician in charge of treatment to principal investigator. Patients with contrast allergy, decreased kidney function, CF-LVAD implantation less than one month ago and unstable patients requiring intravenous inotropes are excluded.
Furthermore we will seek information on the inclusion criteria and make sure that patients are 18 years or older. If all criteria are met we will supply the patient with written information introducing the study and offer the patient to be included in the study.
The investigator will be responsible for:
-Trial participants receiving adequate information on the purpose, metod, advantages and risks associated with participating in the trial (orally and in writing). Before participants are included an informed written consent will be collected. Participants are furthermore informed that it is possible to withdraw from the trial at any given time without any explanation and that this decision will have no effect on future treatment and follow-up.
-That the participant has the opportunity to ask questions and are allowed time to consider the given information. The information will be given in a quiet setting and without any pressure. The participant will be offered to bring a third party under the process of information.
-Before any trial procedures are initiated the participant must sign a dated informed consent. The investigator will safely store the original written consent and the participant will receive a copi of this. The group and the Ethics Committee have to approve a revised version in case of any modifications to the protocol.

Procedure for obtaining informed consent
The contact to the participant will take place from The Department of Cardiology B, Rigshospitalet. A written consent to participate is made when the participant has a comprehensive picture of the given information and after the required time for consideration to acceptance. This consent will be given to Dr Mette Holme Jung or Dr Kiran Mirza, The Department of Cardiology B, Rigshospitalet.